later by many other authors, and which has come to be known as the "Bacteriophage." It is unnecessary here to go into the theories as to the nature of the "Bacteriophage" and its exact relationship to the lytic substance we have described (lysozyme). The extreme rapidity of its action, the wide range of temperature through which it will act, the fact that it will dissolve dead as well as living bacteria, the difficulties experienced in passing small quantities through a porcelain filter, and the absence in solid cultures of the small clear areas of lysis, mark out lysozyme as something different from the bacteriophage.

Summary.

Strains of *M. lysodeikticus* resistant to lysozyme action can readily be developed.

The resistance is not specific, *i.e.*, strains made resistant to one tissue or secretion are equally resistant to all tissues, whether derived from man, the lower animals, or from vegetables, showing that the lysozyme affecting *M. lysodeikticus* is the same whatever is the tissue it is derived from.

After solution of a large number of *M. lysodeikticus* there is an increase in the lytic power of the fluid, and this increase affects wholly or mainly the homologous microbe.

The Pigmentary Effector System.—II.

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(Communicated by Prof. E. W. MacBride, LL.D., F.R.S. Received August 1, 1922.)

(From the Zoological Laboratory, Imperial College of Science.)

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1. *Introduction.*

In a previous paper dealing with the pigmentary response evoked by pituitary (posterior lobe) administration in the common frog, emphasis has been laid on the necessity of discriminating between the alternatives of nervous and endocrine factors in controlling colour changes in Amphibia. In the present communication some account of the pigmentary responses evoked by physiological reagents is discussed, before passing on to more direct methods of experiment. To investigate the action of drugs on melanophores, the ideal method would be to study the effects of the latter on the isolated skin. In common with other investigators, we have, however, found that when frog's skin is placed in Ringer's solution a condition of extreme melanophore contraction supervenes, so that this mode of treatment is useless for demonstrating the action of drugs whose application induces expanded melanophores to contract. As Spaeth, who has studied the effect of drugs on the melanophores of fish scales, rightly insists, the administration of drugs to the intact animal is fraught with formidable objections. But the disadvantages are pre-eminently of the nature of limitations. Of these the most obvious are: first, the difficulty in discriminating between local, peripheral, central, or reflex effects, when the seat of action of the drug is not homogeneous, *e.g.* in the case of atropine which has peripheral (parasympathetic) as well as central effects, or of veratrine, which acts directly on contractile tissue, and reflexly through its excitatory effect on sensory nerve endings; secondly, the possibility of inducing death, or interfering unduly with the circulation, with quantities subminimal to produce pigmentary response. However, if these limitations are recognised, the study of drug administration can, in the light of existing pharmacological knowledge, be used to explore the possible existence of a nervous mechanism of control in colour change.

In this connection both direct experiment and the study of drug administration, have prompted a bewildering series of conflicting statements from a body of investigators so numerous that it is impossible to mention them individually. Fuchs, in his extensive survey of the literature—there are about 150 papers on Amphibian pigmentary changes—comments upon this lack of unanimity: "Wir müssen diese verschiedene Reaktionen auf ein und dasselbe Reagens als physiologische Artverschiedenheiten ansehen." Foremost among those who have studied pigmentary responses to drugs in Amphibia are Biedermann, Bimmermann, Carnot, and Fuchs (1906). The reagents investigated by previous workers include veratrine, strychnine, santonin, curare, brucine, coniine, morphine, atropine, and eserine; but none have systematically applied modern knowledge of pharmacological reagents, using those whose action is most instructive. Apart from Lieben's important work (1906) on adrenalin, the only observation which is specially interesting is Fuchs' discovery that nicotine in amount adequate to produce motor paralysis induces darkening of the frog's skin.

To demonstrate expansion of the melanophores, frogs rendered pale by being placed in dry glass dipping jars on a white background at laboratory temperature (70° F.) in a well-lighted situation, were employed. To show contraction of expanded melanophores, frogs of approximately 20 grm. by weight were kept in receptacles with darkened sides containing a small quantity of water. The research was carried out in Prof. MacBride's laboratory, and expenses were defrayed by a grant from the Government Grants Committee of the Royal Society.

2. *The Action of Drugs.*

The experiments which follow were carried out on intact animals (except where otherwise stated), by intraperitoneal administration of drugs. The method employed for inducing pallor, or darkening before experiment, has been already outlined above.

Experiments on Darkened Animals.—The experiments carried out on darkened animals were made in two series. In one series of experiments the animals were placed for several hours previous to injection in receptacles with darkened sides containing a small quantity of water. In these experiments, controls were injected with Ringer's solution to explore the possible effects of "excitement." The treatment was not found to induce melanophores to contract, and this source of error may therefore be dismissed. In the second series, dry animals kept on a light background were darkened by an injection of pituitary extract approximately of minimal magnitude, the actual dosage being 0·0003 c.c. of Burroughs Wellcome's liquid sterile preparation "Infundin." In such minute quantities pituitary injection does not maintain the melanophores in an expanded condition for more than 1½—2 hours. Injection of the drugs employed was therefore made half an hour after pituitary injection in each case. A comparison of two such series seemed desirable, since any disparity between the subsequent action of drugs in animals darkened by natural factors, on the one hand, and by pituitary administration on the other, would create a formidable objection to an hypothesis which regarded the pituitary melanophore response as a significant factor in the mechanism of pigmentary changes created by normal environmental stimuli. As will be seen from the accompanying table, in which the experimental data are set forth, the results obtained in both series were entirely consonant. It is worth mentioning that the melanophore contraction which follows administration of ergotoxine is peculiarly protracted, lasting in some cases for several days. Unlike Fuchs, we did not find that veratrine induced certain contraction in darkened frogs. Certain drugs were employed in a somewhat limited range of dosage, and negative results observed with them should not therefore be insisted upon too dogmatically.

Drug.	Animals darkened by natural means.		Animals darkened by pituitary injection.	
	Doses.	Effect.	Doses.	Effect.
	mgrm.		mgrm.	
Tyramine	10–5	Pallor	10–5	Pallor
	2	No effect	2	No effect
Ergotoxine	0·6, 0·3, 0·06	Pallor (prolonged)	0·6, 0·3, 0·06	Pallor
Histamine	3, 1·5, 0·5	No effect	3, 1·5, 0·5	No effect
Caffeine	7·5–1·5	Pallor	7·5–1·5	Pallor
Barium chloride	1–0·2	No effect	1–0·2	No effect
Sodium nitrite	7·5–1·5	,,	7·5–1·5	,,
Digitalin	0·6–0·3	,,	0·6–0·3	,,
Veratrine	1/10–1/50	,,	1/10–1/50	,,
Pilocarpine	15–3	,,	15–3	,,
Atropine	1–3–5	,,	1–3–5	,,
Cocaine	¼, ⅔, 1½	Pallor	¼, ⅔, 1½	Pallor
Ringer's solution	0·5 c.c.	No effect	5 c.c.	No effect

Experiments on Pale Animals.—The results obtained by administration of drugs to pale animals are significant as illustrative of the remarkable specificity of pituitary extracts in promoting the expansion of the dermal melanophores. As is well known, the excitatory action of posterior lobe secretions upon plain muscle and blood-vessels is shared by a group of well-known drugs (*e.g.* histamine, $BaCl_2$, and digitalis especially). In the melanophore response evoked by pituitary extracts, on the other hand, we have to deal with a reaction which is not precisely simulated by any of the more familiar physiological reagents. The following Table summarises the experimental data :—

	Mgrm.	Mgrm.	Mgrm.	Remarks.
Atropine	10	3	1	No effect on colour.
Pilocarpine	25	12·5	1	,, ,,
Histamine	3·6	0·36	0·036	,, ,,
Ergotoxine	6·5	0·65	0·065	,, ,,
Tyramine	20	2	0·2	,, ,,
Veratrine	¼	1/20	1/100	,, ,,
Caffeine	10	2	—	,, ,,
Barium chloride	1	1/5	—	,, ,,
Sodium nitrite	5	—	—	,, ,,
Strychnine	1	1/25	1/100	,, ,,
Digitalin (water soluble, Parke Davis)	0·9	—	—	Death within an hour, no colour change.
	0·5	—	—	Usually fatal, with partial darkening two hours after injection in some cases.
	0·3	—	—	No effect on colour.

Whether digitalis would affect the melanophores in higher concentration than those which no longer permit the heart to function satisfactorily normally does not appear; but no effect was discovered on isolated skin. While none of the above drugs were found to induce melanophore expansion, the injection of nicotine, as already shown by Fuchs, and of apocodeine, can, if the dosage is properly adjusted, be made to bring about a darkening of the frog's skin which is readily visible, but not associated with such a complete expansion of the melanophores as that which accompanies pituitary administration.

Action of Nicotine.—A series of pale frogs were injected with nicotine as follows:—A 1—4, 2 mgrm.; B 1—4, 1 mgrm.; C 1—4, $\frac{1}{2}$ mgrm.; D 1—4, $\frac{1}{4}$ mgrm.; E 1—4, 1/8 mgrm.; F 1—4, 1/12. The first dozen frogs (A—C) displayed motor paralysis, after the lapse of $\frac{1}{2}$—$\frac{3}{4}$ of an hour. The A series were considerably darker; microscopic examination showed that the dermal melanophores were expanded. In the B and C series a slight visible darkening was noticed at the end of half an hour, but on microscopic examination only the epidermal melanophores were found to be expanded. The remaining animals showed no pigmentary changes. Thus darkening of the skin was found only where doses more than sufficient to produce general motor paralysis were administered. In all cases the heart was found to be beating when the animals were killed for microscopic examination of the skin.

Action of Apocodeine.—Five pale frogs were injected respectively with 15 mgrm., 12·5 mgrm., 10 mgrm., 7·5 mgrm., 5 mgrm. The first two displayed complete motor paralysis with expansion of the melanophores after three-quarters of an hour. The two frogs injected with 10 mgrm. and 7·5 mgrm. displayed partial motor paralysis without very noticeable pigmentary change. The last frog did not display motor paralysis, and remained quite unchanged with respect to bodily coloration. The similarity between the action of apocodeine and nicotine in producing melanophore expansion in doses above that required to induce motor paralysis is thus very close.

3. *The Action of Adrenal and Pineal Extracts.*

The important work of Lieben (1906) has already been mentioned. Lieben also worked on *R. temporaria*, keeping his animals in the dark at 2° C. to ensure melanophore expansion. He found that melanophore contraction followed injection of adrenalin, beginning 6 minutes later, and reaching its maximum effect in about half an hour. In one respect only do our observations fail to confirm those of Lieben, who found that both intravenous and intraperitoneal injection produced contraction of the melanophores, though in the latter case vaso-constriction did not accompany the pigmentary response. We, on the contrary, only obtained the pigmentary reaction by intravenous injection, as the following experiment indicates:—Six darkened frogs were injected intravenously with 2 mgrm. of adrenalin dissolved in Ringer's fluid, six other darkened animals each received a similar dose by intraperitoneal injection, while six controls received an intravenous injection of Ringer's fluid alone (*viâ* the anterior abdominal vein). At the end of 10 minutes the first six were all pale. The remaining animals showed no pigmentary change.

In view of the observations of McCord and Allen, confirmed later by Huxley and Hogben, the administration of pineal extracts was essayed with dark frogs, but neither intraperitoneal nor intravenous administration of fresh or commercial preparations proved efficacious to induce melanophore contraction.

The most significant point which emerges at this stage in the investigation is that, with the exception of caffeine, the only drugs which have been found by us to induce melanophore contraction are those which are known to produce peripheral sympathetic stimulation; while, with the exception of pituitary extracts, the only drugs found to bring about melanophore expansion were nicotine and apocodeine, in amounts sufficient to produce general peripheral paralysis of sympathetic nerves. The fact that adrenalin and tyramine are opposed to the action of pituitary extract, while histamine has no effect on melanophores, is of special interest, in view of the criticism raised in certain quarters to the effect that pigmentary reactions are merely the outcome of vasomotor influences.

4. *The Effects of Nerve Section.*

Until lately the possible existence of an endocrine mechanism of pigmentary control was unrecognised. Earlier workers on colour response in Amphibia directed their attention exclusively to the nervous factor. It has been seen in the preceding section that the results of drug administration to the intact frog offer indirect evidence that the melanophores are innervated by a sympathetic nerve supply tending to promote the contraction phase. But more direct evidence is difficult to obtain. The methods adopted by previous workers are by no means conclusive in the light of existing knowledge concerning the reaction of melanophores to the adrenal and pituitary autacoids, and they are far from being unanimous.

The technique employed in the past includes: (*a*) destruction or transection of the cord or brain; (*b*) electrical stimulation of the C.N.S.; (*c*) section of peripheral nerve trunks. Lister, Leydig and Bimmermann describe darkening of the skin after destruction of the cord. Hering claimed that transection of the cord in the brachial region was accompanied by melanophore expansion; Biedermann records a transient darkening, while both Carnot and Bimmermann failed to observe any pigmentary change after severing the cord in the brachial region. Concerning the effect of transection of the medulla, the observations of Carnot and Biedermann are again in conflict; and none of the foregoing experiments took into account the relation of the C.N.S. to adrenal secretion. The same criticism applies to the experiments of von Wittich, Biedermann and Dutartre, in which pallor was induced by electrical stimulation of the cord. Steiner and Biedermann went so far as to locate a " centre " for pigmentary control in the mid-brain. As, however, the pituitary of the frog contains an effective reserve (*vide infra*) adequate to produce darkening in fifty individuals, one would require very clear assurance that manipulations which involve destruction of that region of the brain which lies just above the hypophysis were carried out without disturbing the latter. Actually, these workers were ignorant of the necessity for any precautions of this nature. Concerning the effect of severing peripheral nerve trunks there is further disagreement. According to von Wittich, Lister, Hoyer and Hering, and Bimmermann, destruction of the spinal nerve supply in one leg induces a local darkening of the skin. This is denied by Nussbaum and by Hooker, whose results and conclusions are thus summarised: " Severing the lumbosacral plexus or removal of the lower sympathetic ganglia does not affect the normal and synchronous change of colour in *Rana fusca.* When, however, both of these processes are carried out together, the lamed part is at first slower in reacting than the normal. . . . These results demonstrate that there are two nerve centres for the control of the melanophores, one spinal, the other sympathetic. The function of nervous control is to produce a synchronous change in colour over the entire animal." The reader may judge how far the interpretation advocated by Hooker exceeds the legimitate limits of inference.

Experiments on Section of Nerves.—The ambiguity of the evidence derived from transection of the C.N.S. in the light of the adrenalin reaction has been indicated above. Unfortunately, it is not possible to remove the entire adrenal secreting mechanism from such an animal as the frog. In view of the conflict of evidence respecting the section of peripheral trunks, the following experiments were carried out:—

(*a*) The lumbosacral plexus was severed on the right side of the body in two frogs previously anæsthetised with chloroform. After stitching of the wound and subsequent recovery, the animals were kept under observation for several days in a dry illuminated situation. At no time was any difference detected either in visible coloration or in the state of the melanophores in the web as revealed by microscopic observation.

(*b*) The skin of the back in *Rana* is supplied by the rami cutanei dorsi mediales and laterales; the former traverse the lymph sac freely, while the latter run in the lateral septum which bounds the dorsal subcutaneous lymph space. In two frogs the rami cutanei dorsi mediales were severed by making an incision just above the anus sufficiently large to admit the insertion of a fine pair of dissecting scissors. In two other frogs the lateral septa, and therewith the rami cutanei dorsi laterales, were cut through, an incision being made for the purpose through the posterior extremity of the abdominal skin. The operations were performed under anæsthesia, and the folds of the skin bounding the incision stitched together in each case. As in the previous experiment, the animals were kept under observation in a dry illuminated situation for two days, remaining uniformly pale. It is probable that in the last-mentioned experiments the entire nerve supply of the skin of the back was severed, and, in view of the darkening produced by nicotine and apocodeine, the results obtained are decidedly disappointing. It must be remembered, however, that the operation involved considerable disturbance of the cutaneous blood supply, and there are various indications that anæmia interferes with melanophore reactions. However that may be, there are further objections to accepting these experiments as inimical to the hypothesis that the melanophores are under nervous control. If the melanophores are innervated by fibres tending to induce contraction, the first effect of severing the nerve would presumably be to to induce contraction. Now Redfield has recorded evidence that pallor in reptiles is associated with increased secretion of adrenalin, which is known to act on plain muscle even after the degeneration of its sympathetic nerve supply, so that the synchronous maintenance of pallor throughout the body may well be due to adrenal secretion.

Experiments on Peripheral Stimulation.—The consequences of electrical stimulation in peripheral trunks have been omitted from the foregoing *résumé*. Here, again, the testimony of different investigators is conflicting. According to several workers, among whom may be mentioned Bimmermann, Biedermann, Lieben and Fuchs, melanophore contraction ensues in the frog's web after stimulation of the sciatic nerve. Hering, on the other hand, failed to confirm this observation, and others, including Meyer and Ehrmann, deny that stimulation of the sciatic is accompanied by any pigmentary response in the leg.

The method adopted in these experiments to obtain further light on these conflicting indications was as follows:—A glass trough, 7 cm. deep, wide enough and sufficiently long to contain the body of a full-sized frog, was partly filled with wax, allowed to solidify, and bored at one end with two circular holes 1·25 mm. wide and the same distance apart, so that the web of each limb might be stretched out with pins in a manner appropriate to microscopic observation. The trough was placed on the stage of a microscope, with a clamp to hold in position electrodes from an induction coil. The condition of the melanophores in the web of each limb could thus be kept under continuous observation. Three types of preparations were used:—

(*a*) Two dark frogs were anæsthetised with chloroform. The sciatic of each side was severed above the hip and exposed to the knee. The nerve of one side was stimulated over a period of 15 minutes, with appropriate intervals, to prevent total fatigue. At the end of half an hour the melanophores in both webs were equally expanded. The experiment was repeated with similar results (frogs killed at conclusion of experiment).

(*b*) A dark frog was killed by decapitation. The sciatic was exposed to the knee on either side, and the limb severed at the distal end of the thigh. The isolated limbs were prepared for observation, and the sciatic nerve of one stimulated as above. At the end of half an hour the melanophores in the web of the limb stimulated were slightly less expanded than in the control, though there was no noticeable difference at the end of quarter of an hour. After an hour *post-mortem* contraction ensued. The experiment was repeated with similar results.

(*c*) The above procedure was adopted in all respects, save the introduction into the trough of sufficient curare to prevent muscular contraction after nerve stimulation of the isolated limbs. The sciatic of one limb was stimulated continuously for 20 minutes, at the end of which period no difference could be detected in the state of the melanophores of the two limbs. The slight difference observed in experiments (*b*) may well be due, therefore, to the presence of acid products of muscle metabolism; in any case neither the magnitude nor rapidity of the response are comparable to the effect of adrenalin. We are, therefore, of the opinion that, if a nervous mechanism of pigment control exists in the frog, the fibres supplying the melanophores of the web must be identified with those sympathetic neurones which are not incorporated in the sciatic nerve. *Thus the evidence for a nervous mechanism of control is much less direct and conclusive than that available with reference to the influence of endocrine factors upon pigment response.*

5. *Discussion.*

At this stage it is advisable to survey briefly the ground hitherto traversed In a paper (in the press) extending previous work on the pituitary melanophore stimulant recorded in the first paper of this series, certain points emerged which are significant to our present theme, especially: (*a*) that sufficient secretion can be extracted from the pituitary of a single frog to induce melanophore expansion in fifty or more individuals of the same species; (*b*) that the duration of melanophore expansion is more protracted after large doses of pituitary extract than when minimal quantities are administered.

We mention the first of these in connection with the claim of those workers who attempted to identify a "centre" for pigmentary control in that region of the brain lying immediately above the pituitary gland by the use of methods which almost inevitably involved the liberation of pituitary secretion into the circulation. It is thus by no means surprising that these investigators by disturbing the area in question were able to detect a subsequent darkening of the skin.

Though the new facts relating to response of melanophores to drugs set forth in this communication are suggestive, it must be admitted that the case for a nervous control of melanophore reactions is at present unproven. It therefore becomes necessary to consider the hypothesis that the synchronous colour changes of Amphibia are maintained by endocrine influences. On behalf of this alternative there are now two outstanding data upon which to build, namely, the opposing action of the adrenal and pituitary autacoids in producing respectively contraction and expansion of Amphibian melanophores. Furthermore, the time relations of melanophore response to normal environmental stimuli are fully compatible with such an hypothesis. Dark frogs when removed to a situation which promotes melanophore contraction never assume complete pallor in less than half an hour, while adrenalin produces the same result within 15 minutes. Similarly pale frogs subjected to conditions calculated to induce darkening of the skin never display full expansion of the melanophores in less than an hour, whereas the injection of pituitary extract leads to a maximum effect in the same sense within 20 minutes (intravenous). Thus the rapidity of colour change in neither direction presupposes a mechanism other than the accumulation of a minimum quantity of the appropriate secretion.

There are, moreover, two significant facts which are specially suggestive in connection with the action of the pituitary autacoid. These are, first, the uniqueness of the response itself, which is indeed shared only by apocodeine and nicotine in quantities more than adequate to produce general peripheral paralysis of the sympathetic system. Actually the expansion which follows the administration of the last-named drugs is not as complete as the type of reaction which can be evoked by pituitary extract. In any case there are two cogent considerations which conflict with the possibility that melanophore expansion in the intact frog is brought about through the central inhibition of nervous stimuli: (*a*) The failure of experiments on severing the nerve supply of the skin to induce local melanophore expansion; (*b*) the inefficacy of nicotine to produce the same result when administered in doses sufficient to paralyse the sympathetic ganglia, although efficacious when given in quantities adequate to paralyse the peripheral nerve endings, and thereby, presumably, to prevent the normal action of adrenalin. The second point which has emerged in this enquiry is the close correspondence between the effect of drugs administered to frogs in which darkening had been produced, on the one hand by injection of pituitary extract, and on the other by the action of normal environmental stimuli.

If the hypothesis that pituitary secretion is a significant factor in the pigmentary responses of Amphibia is sustained by our subsequent enquiries, a method of experimental control of posterior lobe activity in the intact animal will become available.

6. *Summary.*

1. The existence of a nervous mechanism of pigment control is explored in the light of experiments on the section and stimulation of nerves and the administration of drugs.

2. Apart from caffeine, the only reagents found to induce melanophore contraction were those known to excite peripheral sympathetic nerve endings, namely, adrenalin, tyramine, ergotoxine and cocaine.

3. Apart from pituitary extract, the only reagents found to bring about melanophore expansion were apocodeine and nicotine in quantities sufficient to paralyse all sympathetic nerve endings.

4. No unequivocal direct evidence has, however, been advanced, either in this investigation or by previous workers, to demonstrate a nervous control of pigment responses in Amphibia.

5. The possibility is indicated that the synchronous colour changes of Amphibia in response to normal environmental stimuli are determined mainly by endocrine influences.

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For further reference the first paper of this series may be consulted, as also the extensive bibliography of Fuchs (1914) in the 'Handbuch der Vergleichenden Physiologie' (Jena), pp. 1548–1553.

CROONIAN LECTURE:—*On the Mechanism of Heredity.*

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(Lecture delivered June 1, 1922.—MS. received August 3, 1922.)

[PLATES 7 AND 8.]

Several years ago I ventured to state that with the demonstration of the wide applicability of Mendel's two laws, and with the later discoveries of linkage and of crossing-over, the traditional problem of heredity had been solved. On account of this statement, I have been rebuked for arrogantly affirming that there was nothing more to be learned about heredity!

Perhaps I had given less offence if I had made clear that I realised, as fully as another, that these discoveries in heredity were of such a sort that a whole new world for investigation opened before us. My critics, however, attempted to put me in the wrong by pretending that I implied that there were no new worlds to conquer. It may, therefore, not be out of place to attempt to show how the solution of the traditional problem of heredity has led to further discoveries, and has given us a glimpse at least of still newer problems that may in time lead to even more far reaching consequences.